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A practical guide to reducing/eliminating red blood cell transfusions in the neonatal intensive care unit

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ABSTRACT

Red blood cell transfusions can be lifesaving for neonates with severe anemia or acute massive hemorrhage. However, it is imperative to understand that red cell transfusions convey unique and significant risks for neonates. The extremely rare risks of transmitting a viral, bacterial, or other microbial infection, or causing circulatory overload are well known and are part of blood transfusion informed consent. Less well known, and not always part of the consent process, are more common risks of transfusing the smallest and most immature NICU patients; specifically, multiple transfusions may worsen inflammatory conditions (particularly pulmonary inflammation), and in certain subsets are associated with retinopathy of prematurity and neurodevelopmental delay. Instituting non-pharmacological transfusion-avoidance techniques reduces transfusion rates. Pharmacological transfusion-avoidance, specifically erythropoietic stimulating agents, further reduces the risk of needing a transfusion. The protocols described herein constitute an efficient and cost-effective transfusion-avoidance program. Using these protocols, many NICU patients can remain transfusion-free.

1. Why eliminating/reducing NICU RBC transfusions is an important goal

1.1. Safety of the blood supply

The blood supply in the United States, indeed in all technologically advanced nations, is safer than it has ever been [1]. Transfusion acquired infections, and transfusion errors leading to adverse outcomes, are extremely rare events [2]. The possibility of TACO (transfusion associated cardiac overload) should be considered before and during every transfusion, and the rate of infusion diminished or halted if signs of cardiac overload appear [3]. Similarly the possibility of TRALI (transfusion associated acute lung injury) must be considered with every transfusion where respiratory distress increases during or after the procedure, although this diagnosis is uncommonly made in neonates [4]. The risks of infection, risks of transfusion errors, and risks of TACO and TRALI, though all real, are all rare and should not be used as reasons to withhold a NICU transfusion that is potentially lifesaving.

1.2. Instances where red blood cell transfusion of a NICU patient is imperative

Acute perinatal/neonatal hemorrhage can be so massive that transfusion is unquestionably indicated and is possibly the only hope for survival [5]. Massive blood loss can result from fetal to maternal hemorrhage [6], rupture of an umbilical vessel [7], rapid subgaleal hemorrhage [8], or a dislodged umbilical catheter [9]. When acute blood loss results in severe hypotension, acidosis, and shock, emergent transfusion of low-titer type O whole blood (LTOWB) should be given if available [10]. If LTOWB is not available, serial component transfusions (via a massive transfusion protocol) are indicated [5]. For infants born at birthing facilities without access to a blood bank, rapid transfer to an appropriate NICU should be arranged.

Infants born after significant acute hemorrhage who remain acidotic after re-expansion of their circulation have a need for PRBC transfusions in the first day of life, to provide an immediate increase in oxygen availability. In contrast, infants born following chronic fetal-maternal hemorrhage may be well compensated, despite significantly low hematocrit levels. Care should be taken to perform a partial volume exchange transfusion, replacing a portion of the infant's "low hematocrit"

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Table 1
NICU red blood cell transfusion guidelines, University of Utah and Intermountain Health.

Product	Condition	Indication	Treatment
LTOWB[a]	Massive hemorrhage	Emergency-release whole (trauma) blood	30+ mL/kg
PRBC	ECMO[b] or cyanotic heart disease[c]	Hgb <10–12 g/dL (Hct <30–36 %)	15–20 mL/kg over 2–4 h (may be divided into 2 aliquots of 10 mL/kg each)
	Mechanical ventilation	Hgb <9 g/dL (Hct <27 %)	
	CPAP with supplemental O2; undergoing general surgery	Hgb <8 g/dL (Hct <24 %)	
	Room air	Hgb <7 g/dL (Hct <21 %)	

PRBC, packed red blood cells.
[a] LTOWB (low-titer, type O negative, whole blood), if available, as part of a Massive Transfusion Protocol.
[b] Comparison of transfusion thresholds during neonatal extracorporeal membrane oxygenation. *Transfusion* 2017; 57:2115–2120.
[c] Recommendations on Red Blood Cell Transfusion in Infants and Children with Acquired and Congenital Heart Disease from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediat Crit Care Med* 2018; 19:S137-148.

blood with high hematocrit" PRBCs, in order to avoid congestive heart failure.

Acute and massive blood loss is not the only indication for administering an RBC transfusion to a neonate. When, for any reason, the blood hemoglobin concentration falls below a critical level where delivery of oxygen to organs and tissues is inadequate to support proper function, RBC transfusion can restore adequate oxygenation and improve function. Our University of Utah/Intermountain Health NICU RBC transfusion guidelines are listed in Table 1. These thresholds for RBC transfusion are based on hemoglobin level plus clinical context. We recognize that our guidelines fail to consider the critical issue of adequacy of tissue oxygenation. In the future, identifying and including measures that rigorously evaluate the issue of adequate oxygen availability will greatly improve our guidelines, directing transfusions to those who will most benefit, improving the benefit to risk ratio of transfusion therapy.

1.3. Association between RBC transfusions and development of bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) occurs after immature lungs are exposed to mechanical ventilation, oxygen, and inflammation, but its pathogenesis has not been completely defined [11–13]. We are aware of ten separate studies, between 1997 and the present, assessing a connection between RBC transfusions and the development of BPD [14–23]. As shown in Table 2, all ten found a statistical association between a greater number of RBC transfusions administered and the incidence and severity of BPD. Whether or not this is a *causative* association will be answerable only after completing appropriate large multicentered randomized trials. However, if RBC transfusions do indeed promote the development of BPD, the means of damage might involve a proinflammatory mechanism whereby transfusions exacerbate lung inflammation [24,25].

1.4. Association between RBC transfusions and development of retinopathy of prematurity

Retinopathy of prematurity (ROP) is a disorder of retinal vascularization occurring in preterm infants and is a major cause of childhood blindness [26,27]. We are aware of 12 studies since 2001 demonstrating a statistical association between a greater number of RBC transfusions and higher incidence and severity of ROP [20,28–38]. Table 3 reviews these reports. All 12 found a statistical association between a greater number of RBC transfusions and higher incidence and severity of ROP. If RBC transfusions do indeed promote the development of ROP, a possible mechanism of damage might involve excessive release of oxygen from adult hemoglobin to the developing retina [39,40].

2. Non-pharmacological means to reduce the likelihood of qualifying for an RBC transfusion

The non-pharmacological strategies that will minimize or eliminate RBC transfusions for NICU patients include; 1) ways to start with a larger blood volume and 2) ways to decrease phlebotomy losses. Relatively simple steps can be taken to accomplish both. As listed in Table 4, these include delayed clamping of the umbilical cord after delivery [41–43] and drawing fewer laboratory tests from the neonate [44–52]. The latter can be accomplished by at least three means: 1) obtaining any blood tests needed immediately after birth by using otherwise discarded umbilical cord blood (not blood withdrawn from the newborn infant) [44–48], 2) considering whether every blood test ordered is actually needed and eliminating any unnecessary phlebotomy [49–51], 3) timely removal of the umbilical arterial catheter [52].

Table 2
Associations between number of RBC transfusions received and development of bronchopulmonary dysplasia.

Year	First Author	Journal	Neonates in Study (n) and description	Statistical Findings	Reference
1997	Cooke	Eur J Peds	73 < 34 w	Correlation coefficient, tx and BPD 0.665, p = 0.01	14
2009	Valieva	J Pediatr	60	RBC tx associated with increased risk of BPD (p < 0.05).	15
2011	Zhang	J Pediatr	129 < 1500 g	After 3 RBC Tx odds of BPD 10.2; 95 % CI,2.1–47.6	16
2013	Jeon	Yonsei Med J	50	BPD in 20 (51 %) who received tx vs only 1 (9 %) with similar birth weights who received no tx (p = 0.01).	17
2014	Zhang	Sci Rep	231 < 1500 g	OR for developing BPD after RBC tx 9.8 (95 % CI, 1.7–56.4).	18
2015	Keir	Am J Perinatol	490 < 30 w, RBC after DOL 21	RBC tx at ≥21 days of age in previously transfusion-naive preterm infants associated with increased odds of CLD (1.78; 95 % CI, 1.43–2.22).	19
2017	Ghirardello	Am J Perinatol	641 VLBW 42 % transfused	BPD associated with RBC tx > 3 (5.88, 95 % CI, 2.74–12.6)	20
2019	Patel	Transfusion	598	Greater volume of RBCs tx associated with higher risk of BPD (adjusted relative risk per 20-mL, 1.05; 95 % CI, 1.02–1.07; p < 0.001)	21
2023	Bolat	Am J Perinatol	246	RBC tx number and volume both significant predictors of BPD incidence and severity (p = 0.0001)	22
2024	Bahr	J Pediatr	946	BPD grade increased by 1 for every 2.7 RBC tx (95 % CI, 2.33–3.05; p ≤ 001).	23

w, weeks' gestation; g, grams; tx, transfusion; BPD, bronchopulmonary dysplasia; RBC, red blood cell; CI, confidence interval.

Table 3
Associations between number of RBC transfusions received and development of retinopathy of prematurity.

Year	First Author	Journal	Neonates in Study (n) and description	Statistical Findings	Reference
2001	Dani	Early Hum Develop	45 < 1250 g	RBC tx volume during the first week (OR 1.16; 95 % C.I. 1.03–1.3) and during the first 2 months (OR 2.93; 95 % CI, 1.52–5.62), were associated with ROP	28
2006	Yanovitch	J AAPOS	259 screened for ROP	RBC tx > 7, predicted ROP, p = 0.014	29
2013	DelVecchio	J Maternal Fetal Neonatal Med	Before vs after practice change (to diminish RBC Tx)	When RBC Tx rate fell from 14.8 % to 6.3 %, ROP fell from 4.6 % to 2.4 %; OR 1.95, 95 % CI, 1.24–3.07).	30
2017	Wang	Pediatr Neonatol	98 ELBW	Number of RBC Tx within 30 days correlated with risk of developing threshold ROP (odds ratio: 1.27, 95 % CI, 1.04–1.55, p = 0.02).	31
2017	Ghirardello	Am J Perinatol	641 VLBW 42 % transfused	ROP associated with RBC tx > 3 (5.88, 95 % CI, 2.74–12.6)	20
2019	Lust	J Perinatol	126 with severe ROP	91 % who developed severe ROP received an RBC tx in the first 10 d. Early tx associated with severe ROP; adjusted odds ratio 3.8 (95 % CI, 1.8–8.1).	32
2020	Hengartner	Neonatology	178	RBC Tx associated with ROP development, OR 1.081, 95 % CI, 1.02–1.15.	33
2021	Jiramongkolchai	Eye	60	Low HbF levels at 31 and 34 weeks are associated with increased risk of ROP (p < 0.0006)	34
2021	Schecter	J Neonatal Perinatal Med	61 with severe ROP	Laser-treated infants had more RBC tx than non-treated infants (mean tx 22.3 vs. 6.5, p < 0.001)	35
2023	Jiramongkolchai	Br J Ophthalmol	64	Higher HbA levels correlated with increased risk of ROP (p < 0.0001)	36
2023	Uberos	Acta Opthalmol	565 VLBW	ROP risk was 2.77 times higher (95 % CI 1.31–5.88) after ≥3 Tx, with a 3.95 times higher risk (95 % CI, 1.4–11.1) of severe ROP	37
2023	Glaser	Acta Paediatr	12565 infants<29 w	RBC tx associated with increased odds of ROP (OR 1.4, p < 0.001), ROP progression (OR 2.1, p < 0.01) and ROP requiring treatment (OR 3.6, p < 0.001).	38

w, weeks' gestation; g, grams; tx, transfusion; ROP, retinopathy of prematurity; RBC, red blood cell; CI, confidence interval.

Table 4
Non-pharmacological means to reduce the likelihood that a NICU patient will qualify for a red cell transfusion.

Strategy	Intervention	References
Start with a higher blood volume	Delayed umbilical cord clamping	41, 42, 43
	Umbilical cord milking	41, 42, 43
Reduce phlebotomy losses	Draw any blood for initial laboratory studies from otherwise discarded umbilical cord blood	44, 45, 46, 47, 48
	Eliminate unnecessary phlebotomy	49, 50, 51
	Appropriate early removal of umbilical artery catheters	52

3. Administration of erythropoiesis stimulating agents (ESAs) decreases RBC transfusions

Studies over the past 30 years have reported decreased RBC transfusion needs when ESAs such as erythropoietin and darbepoetin are administered. In numerous randomized placebo-controlled trials [53–57] not only are fewer RBC transfusions given to those infants randomized to ESAs, but hematocrits are higher in the ESA group (Fig. 1), representing active erythropoiesis and an increased fetal hemoglobin-containing red cell mass [58].

4. Advantages of using darbepoetin *vs*. erythropoietin to reduce the likelihood of NICU patients qualifying for red cell transfusions

Practical considerations, as well as our own data on outcomes, favor using darbepoetin (when available on formulary) rather than erythropoietin in our Utah pharmaceutical transfusion-reduction program. Pharmacokinetic and dynamic studies support once per week darbepoetin dosing *vs.* three times per week erythropoietin dosing [59–61]. Fewer subcutaneous injections is an inherent advantage. Compared with erythropoietin, darbepoetin treatment requires only one third of the pharmacy preparation charges, and only one third of nursing time required for administration.

In a multicentered prospective randomized trial we randomized 102 infants weighing 500–1250 g at birth to receive either darbepoetin, erythropoietin, or placebo through 35 weeks gestation [53]. We found a relationship between higher peak Epo concentrations and higher

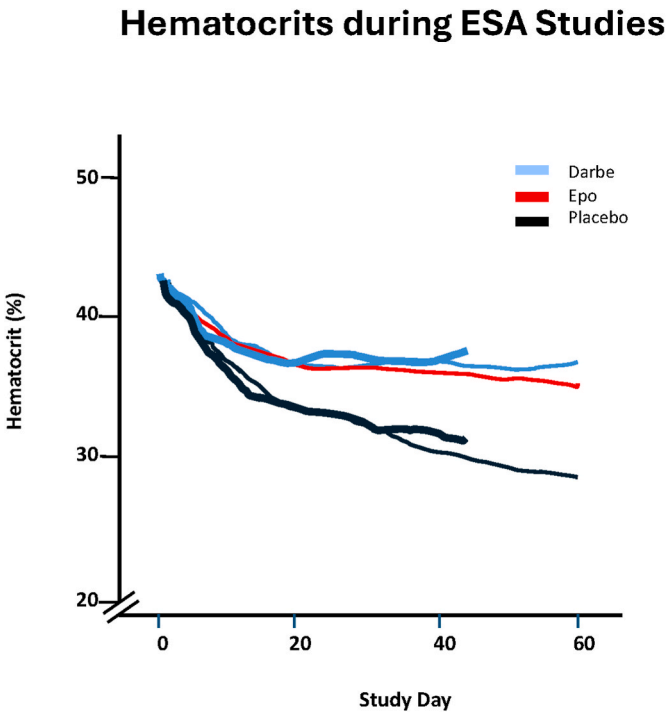

Fig. 1. Changes in hematocrit during ESA administration: Data summarized from two randomized placebo-controlled trials [ref 53 and 57]. Infants randomized to ESAs (darbepoetin [blue lines] or erythropoietin [red line]) had significantly higher hematocrits than infants randomized to placebo (black lines) during the study, despite receiving fewer transfusions.

full-scale IQ at preschool neurodevelopmental follow-up (Fig. 2). (both darbepoetin and erythropoietin are measured in the Epo concentration assay). We found better object permanence scores at 18–22 months in the darbepoetin recipients than in the erythropoietin recipients (Table 5) [62]. Again at 3-to-4-year follow-up, the darbepoetin recipients had better combined overall neurodevelopmental outcomes (Table 6) [63].

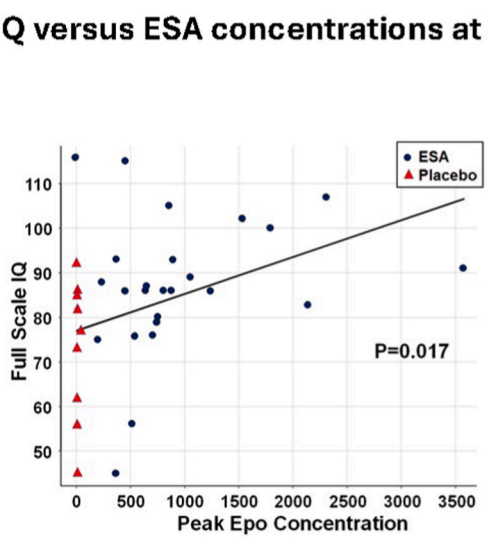

Fig. 2. Preterm infants enrolled in an ESA trial during their NICU hospitalization [ref 53] were evaluated at four years of age. The full-scale IQ at 4 years correlated with peak erythropoietin concentrations measured during the study treatment period (p = 0.017).

Table 5
Neurodevelopmental and neurodevelopmental impairment at 18–22 months (from Ohls RK et al., Pediatrics. 2014; 133(6): 1023–1030 [62].

Outcome	Darbepoetin (n = 27)	Erythropoietin (n = 29)	P Value	ESAs combined	Placebo	P value	Odds Ratio (95 % CI)
Composite Cognitive	96.2 ± 7.3	97.9 ± 14.3	0.61	96.5 ± 11.2	88.7 ± 13.5	0.01	
Composite Language	92.4 ± 13.2	89.9 ± 18.4	0.56	90.7 ± 15.4	83.6 ± 13.1	0.06	
Object Permanence	2.8 ± 0.4	2.4 ± 0.9	0.01	2.6 ± 0.7	2.2 ± 1.0	0.05	
Cognitive Score <85	0 (0)	3 (10)	0.12	3 (5)	6 (25)	0.20	0.17 (0.04–0.75)
Cognitive Score <70	0 (0)	1 (3)	0.50	1 (2)	2 (8)	0.20	0.2 (0.02–2.32)
NDI # and (%)	3 (11)	4 (14)	0.88	7 (12)	10 (42)	0.005	0.2 (0.06–0.62)
Cerebral palsy*	0 (0)	0 (0)	1.00	0 (0)	5 (21)	0.002	NA
NDI or death # (%)	4/28 (14)	5/39 (17)	0.92	9/58 (16)	13/27 (48)	0.002	0.2 (0.07–0.56)

ESA: Erythropoiesis Stimulating Agent; odds ratios are reported with 95 % confidence intervals; [1]Neurodevelopmental impairment (NDI) defined as either cerebral palsy, visual deficit, hearing deficit, or a cognitive score <85. Percentages for neurodevelopmental impairment or death include deaths during initial hospitalization. *Given absence of cerebral palsy in the ESA treatment group, odds ratios cannot be estimated. P-values given for cerebral palsy were computed using Fisher's exact tests for the unadjusted p-value and using ANCOVA with sex as the only covariate for the remaining p-values.

Table 6
Neurodevelopment at 3.4–4.0 years. Follow-up of 24 recipients of erythropoietin and 15 recipients of darbepoetin. Paired assessment of all neurodevelopmental measurements (from Ohls RK et al., Pediatrics 2016; 137:e20153859 [63].

Measurements	Erythropoietin (n = 24)	Darbepoetin (n = 15)	P value
Full-scale IQ	89.6 (19.2)	94.5 (16.1)	0.42
Verbal IQ	93.6 (17.9)	92.1 (16.1)	0.80
Performance IQ	89.6 (19.2)	94.5 (16.1)	0.12
General Language	87.9 (18.0)	92.7 (15.1)	0.41
Executive Function	98.3 (13.5)	102.3 (7.8)	0.49
Working memory	98.3 (17.0)	104.3 (8.9)	0.42
Inhibition	98.4 (16.8)	100.3 (12.7)	0.91
Summary			<0.01 (two tailed)

5. The Utah darbepoetin program

We designed and implemented the Utah Darbepoetin Program with the goal of safely reducing RBC transfusion rates of our NICU patients. Elements of the program are listed in Table 7. Eligibility is focused on preterm infants who are likely to receive one or more RBC transfusions. These include all infants born weighing less than 1000 g, as well as critically ill infants 1001–1500 g at birth. The term "critically ill" is not precisely defined but is generally taken to mean those receiving mechanical ventilation. Additional eligible neonates are those weighing more than 1500 g at birth but having conditions that most likely put them at substantial risk for receiving RBC transfusions, such as those infants with hemolytic disease or early hemorrhage, and preterm or term infants undergoing surgical procedures in the first weeks of life.

The treatment, once-weekly administration of darbepoetin alpha (10 μg/kg body weight) begins within 48 h of birth. Table 7 lists our suggested iron dosing accompanying darbepoetin dosing. We recommend continuing the weekly dose until 34 completed weeks of gestation, or for those at 34 weeks still requiring mechanical ventilate and with a hematocrit <28 %, we continue through 38 weeks.

6. Scheduling "Darbe Fridays" in the NICU

At the University of Utah Hospital NICU, as well as at several of our Intermountain Health NICUs in Utah, we utilize a cost-lowering method in the pharmacy to make darbepoetin available safely and efficiently for the patients who qualify for the Darbe Program. We administer darbepoetin in the NICU only once a week, on Friday. Gloved and under a pharmacy hood, the pharmacist technician divides the contents of the sterile darbepoetin vial aseptically into multiple unit doses, each one being an appropriate dose for one specific patient in the program (Fig. 3). For patients in the first seven days of life who are under a "minimum stimulation" protocol and have a functioning and available intravenous (IV) line, the technician draws the doses from a 25 mcg/mL concentration darbepoetin vial, into 1 mL IV syringes. The bedside nurse then administers the darbepoetin aseptically into the line, as a slow

Table 7
The University of Utah NICU Guidelines for Using Darbepoetin Alfa for Anemia of Prematurity/ Transfusion Avoidance.

Population:

- Infants with birthweight <1000 grams;
- Critically ill infants 1001-1500 grams (expected to have significant phlebotomy losses and anemia of prematurity)
- Infants with congenital anomalies requiring surgery
- Infants born with low hematocrit due to hemorrhage
- Infants with late anemia due to ABO incompatibility or Rh hemolytic disease

AND hematocrit < 50%

Treatment Initiation:

- Begin darbepoetin within 24-48 hours of life.
- Consider a single dose of IV iron 3 mg/kg in first week of life
- Start oral iron when infant is tolerating 60-80 mL/kg/day enteral feeding
-

Medication	Route	Dose	Frequency
Darbepoetin	SQ/IV	10 mcg/kg/dose	Q week
Iron	PO	6-12 mg/kg/day	divide Q 12 hours when ≥8 mg/kg/day

Treatment Course/Monitoring:

- Give darbepoetin as a weekly dose 10 mcg/kg SQ or IV. Darbepoetin may be given as an IV push in babies with IV access in place and little subcutaneous tissue. After the first dose, subsequent doses will be scheduled on Fridays.
- Continue weekly darbepoetin until infant completes 34 weeks gestation. For infants at 34 weeks still requiring significant oxygen/vent support and Hct <28%, may continue darbepoetin through 38 weeks gestation.
- Monitor reticulocyte hemoglobin (RetHe) for Fe sufficiency (goal >29 pg). Check RetHe at 14 days of age. Repeat every 2-4 weeks if adjusting iron dosing. Increase iron by 2 mg/kg (max of 12 mg/kg/day) if RetHe is <29 pg. Decrease iron by 2 mg/kg if RetHe is >35 pg.
- If RetHe is not available, a ferritin concentration <50 ng/mL may reflect iron insufficiency; increase oral iron 2 mg/kg, repeat ferritin every 2-4 weeks.

Treatment Discontinuation:

- Discontinue darbepoetin at 34-38 wks CGA as described above
- Discontinue or hold darbepoetin if Hematocrit is ≥ 50, or for significant thromboembolic disease or hypertension.
- **Do not** hold darbepoetin or iron for an elevated reticulocyte count or blood transfusions (except in the case of double volume exchange transfusion for hemolytic anemia, then hold iron x 2 weeks after transfusion)

push. For all other patients, the pharmacy technician aseptically draws the dose from one 100 mcg/mL concentration darbepoetin vial, into 1 mL TB syringes with needle attached. The bedside nurse administers the darbepoetin subcutaneously. We use the 100 mcg/mL vial, thereby obtaining six to eight doses from the one vial (depending on the weights of the recipients). We label both the IV and subcutaneous products with a beyond use date of 24 h.

Preterm infants receiving darbepoetin are followed closely for signs of anemia, and hemoglobin and reticulocyte hemoglobin values are obtained every two to four weeks to evaluate iron sufficiency.

7. Utah transfusion-free hospital stays associated with the darbepoetin program

RBC transfusion-free rates among preterm infants with a birthweight <1000 g are typically well below 10 % [64,65]. Transfusion-free survival rates increase proportionately with gestational age at birth. For instance, data from the Neonatal Research Network Generic Database for 2021 shows a transfusion-free rate of 25 % for infants born at <29 weeks' gestation who survived at least 12 h [66]. However, over 4-fold differences exist according to administrative site; from a low of 11 % to a high of 48 %. The site with the highest transfusion-free rate is our Utah program.

The altitudes of the hospitals in our Utah NRN sites range from 4298 ft to 4865 ft above sea-level and are the very highest elevation sites in the entire NRN. Theoretically this high elevation of the Utah hospitals could be associated with a need for higher red blood cell transfusion rates, in order for the neonates who are cared for here to achieve adequate oxygenation for optimal health. However, comparison of the 15 NRN sites show our transfusion-free rate to be the highest (Fig. 4). We attribute our high transfusion-free rate to the program described herein; where we recognize significant value in diminishing or eliminating red blood cell transfusions and we employ the non-pharmacological and pharmacological methods described in this review to bring this about.

8. Conclusions

RBC transfusions, when necessary, are a valuable part of newborn intensive care, especially as an emergency both in delivery room and NICU. However, transfusions that have no benefit, other than raising a

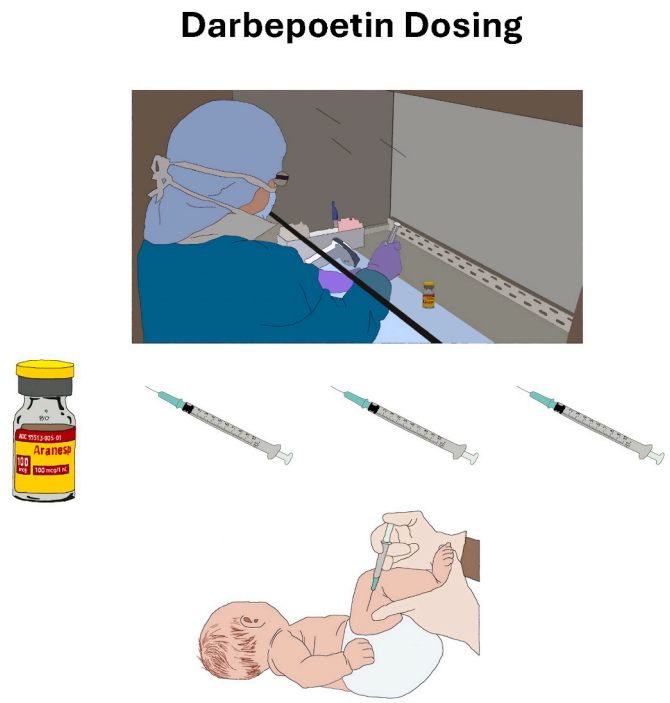

Fig. 3. Illustration of the "Darbe Friday" portion of the Utah Darbepoetin Guidelines. Every Friday the pharmacy technician aseptically opens a vial of darbepoetin and transfers the proper dose to individual sterile syringes; one for each NICU patient who is receiving weekly darbepoetin on this program. Each syringe, containing a dose of 10 μg/kg body weight of the recipient, is barcoded and delivered to the bedside nurse to be administered intravenously or subcutaneously.

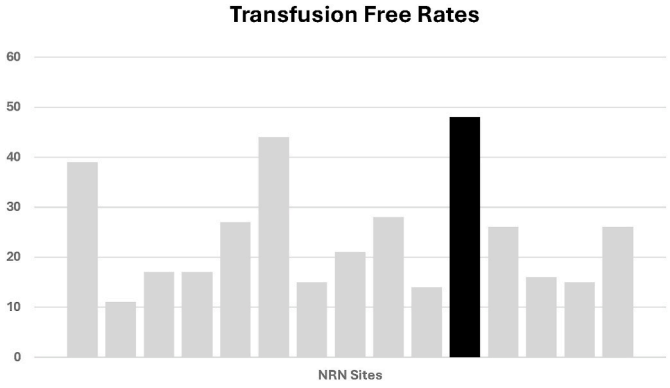

Fig. 4. Percent of preterm infants <29 weeks' gestation who were transfusion-free during 2021. The percentage of infants at our Utah NRN sites (48 %, black column) who remained transfusion free was the highest of all the Neonatal Research Network sites (grey columns).

number in their CBC, subjects those neonates to unbalanced risks; and while some such risks are extremely rare, others are common. Some risks derive from the physiological mismatch involved in transfusing extremely-low-birth-weight neonates with red blood cells obtained from adult blood donors. Erythrocyte size, flexibility, and the type of hemoglobin contained are very different in adult *vs.* fetal blood, and whereas fetal red blood cells are uniquely suited for a fetus, adult red blood cells are not. we realize that until a safe and available source of fetal red blood cells for transfusion is provided, adult donor blood is our only possibility for transfusing those anemic neonates who are truly in need of a higher red blood cell mass.

Meanwhile, effective transfusion reduction programs can be instituted in more NICUs. Doing so will not only reduce the number of transfusions given per transfused patient but will also increase the number of transfusion-free survivors. Following over 30 years of randomized placebo-controlled studies evaluating ESA administration to term and preterm infants at risk for red cell transfusions, the overwhelming evidence for benefit allowed us to create guidelines for darbepoetin administration for a variety of NICU patient populations. The evidence-based guidelines for darbepoetin administration have resulted in a significant decrease in red cell transfusions in the smallest preterm infants and increased the percentage of infants remaining transfusion-free during NICU hospitalization. We endorse the transfusion reduction strategies reviewed herein and encourage their adoption by neonatologists who, like ourselves, place considerable importance on safely reducing erythrocyte transfusions and striving for transfusion-free survival.

These guidelines provide an "indication" where transfusions are thought to have benefits outweighing risks. The guidelines do not mandate that a transfusion *must* be ordered for neonates with this "indication; " rather as reminders to *consider* a transfusion under those circumstances. Any order for blood products should be accompanied by a note in the medical record stating the reason for the transfusion, and consent from family obtained.

Author contributions: CRediT

Robin K. Ohls, Conceptualization, writing – original draft, writing – review and editing, Timothy M. Bahr, Conceptualization, writing – review and editing, Thomas G. Peterson, Conceptualization, writing – review and editing, Robert D. Christensen, Conceptualization, writing – review and editing.

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Declaration of competing interest

The authors have no conflicting interests to declare.

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